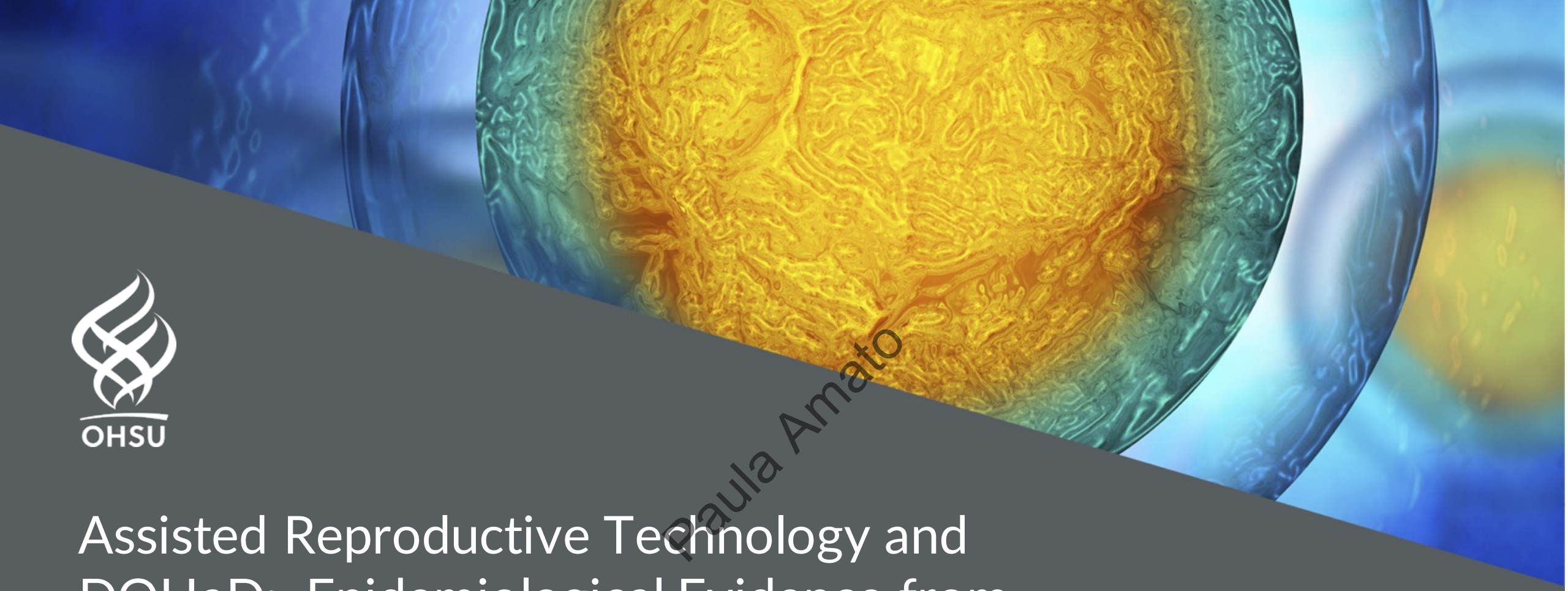
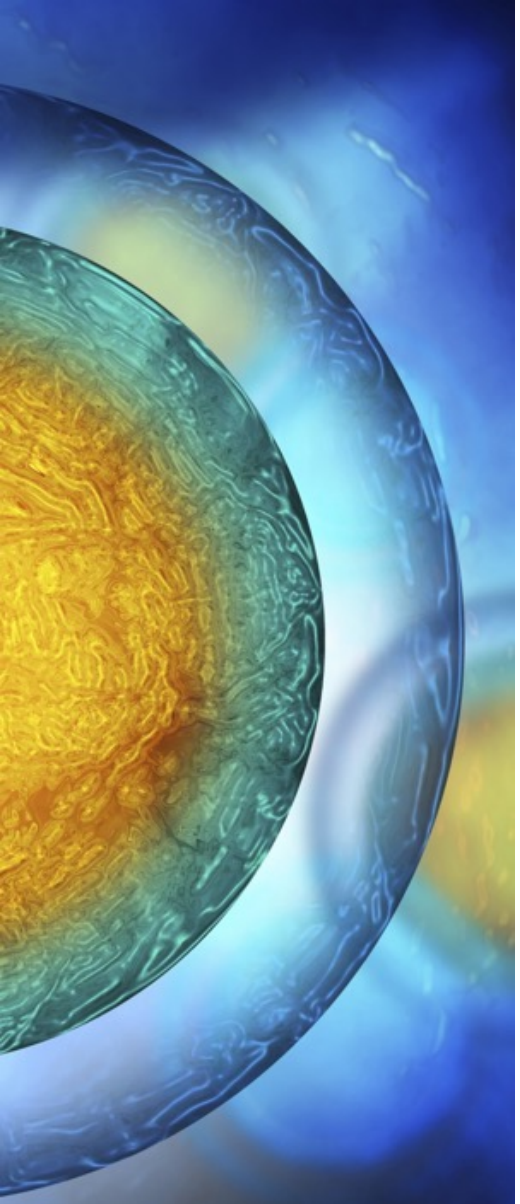


Assisted Reproductive Technology and DOHaD: Epidemiological Evidence from Humans

Paula Amato, MD

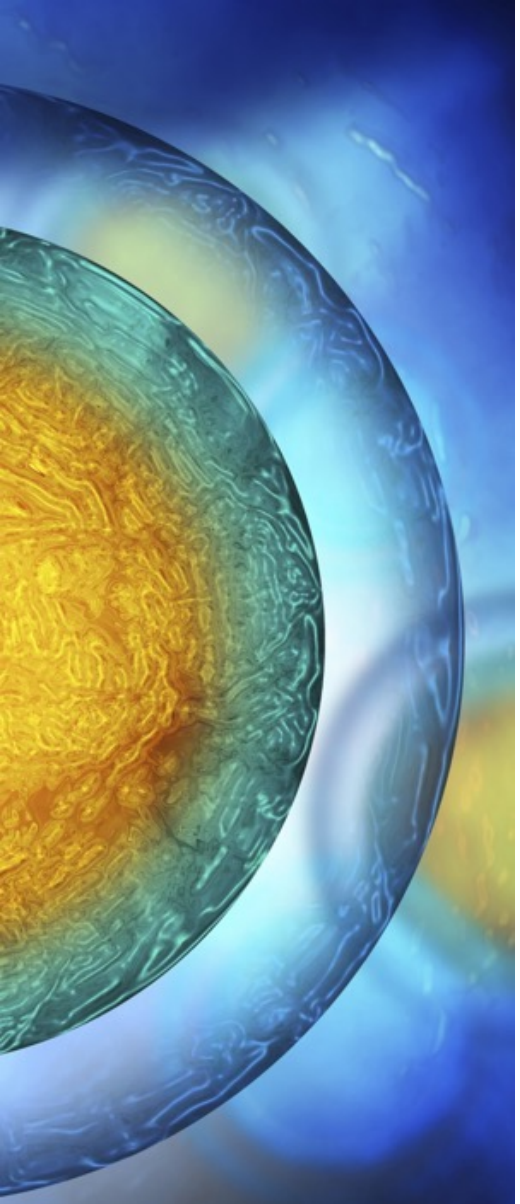
DATE: AUGUST 5, 2021



Disclosures

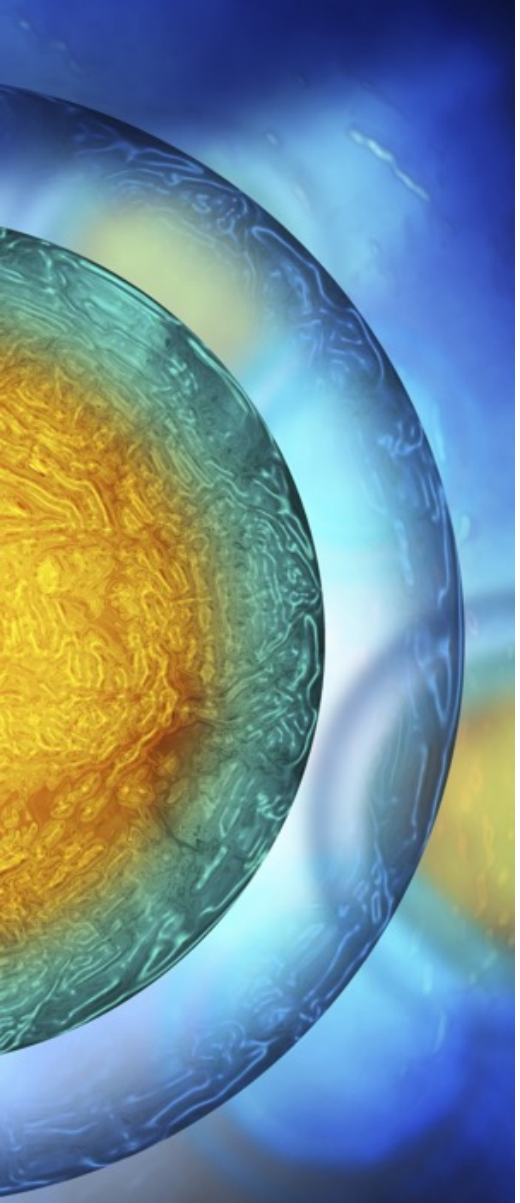
- None

Paula Amato



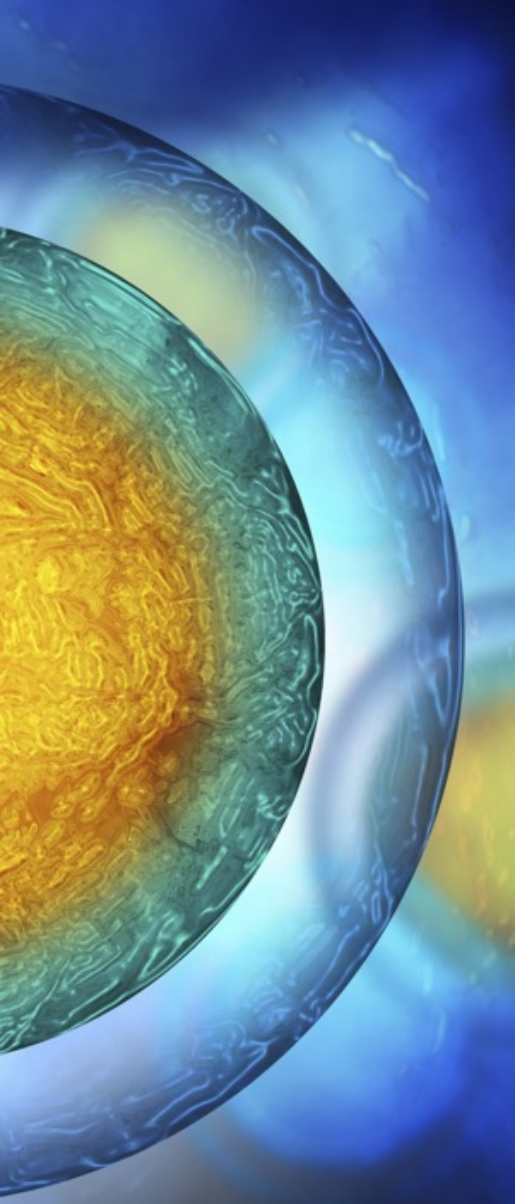
Objectives

- To review the procedures involved in assisted reproductive technology.
- To discuss epigenetic reprogramming during the periconception window.
- To review the epidemiological evidence that ART can increase the risk of cardiometabolic diseases.



ART Timeline & Milestones

- 1953 – first live birth from frozen sperm
- 1978 – first live birth from IVF (Louise Brown; UK)
- 1983 – first live birth from oocyte donation
- 1984 – first live birth from cryopreserved embryo
- 1990s –ICSI, TESE/MESA, PGD, cryopreserved oocyte, IVM
- 2010 – Dr. Robert Edwards awarded Nobel Prize in Physiology/Medicine
- 2014 – first live birth from uterine transplant

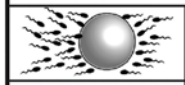


ART Success Rates

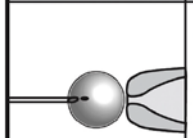
- Over 8 million ART children born worldwide
- Fertility Clinic Success Rate & Certification Act, 1992
- ~ 450 clinics in U.S.
- ~300,000 ART cycles per year (2018)
- ~80,000 children ART children born each year
- ~2% of all infants born in the U.S. each year

In Vitro Fertilization

In vitro fertilization (IVF): Eggs are retrieved from the ovary and fertilization occurs in vitro.

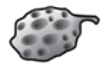


Conventional IVF: Sperm are added to culture medium containing eggs for insemination.

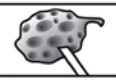


Intracytoplasmic sperm injection (ICSI): A single sperm head is injected into the cytoplasm of the egg. Used for: male factor infertility, if sperm have been obtained surgically, a history of unsuccessful cycles, procedures using either cryopreserved sperm or eggs, and/or if PGD/PGS will be performed. 69% of ART cycles in the United States utilized ICSI.

Associated Procedures



Controlled ovarian hyperstimulation (COH): Hormones are administered to stimulate the maturation of several oocytes. Protocols vary. More than 99% of ART cycles in the United States used ovarian stimulation.



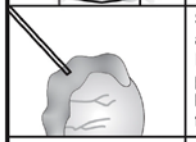
Oocyte retrieval: Eggs are collected by transvaginal ultrasound-guided follicle aspiration.

Embryo culture: Zygotes are cultured for 3 or 5 days using commercially-available culture medium in a 37°C incubator with low oxygen.

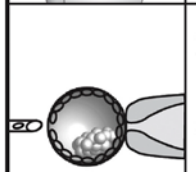
Embryo transfer: Embryos are non-surgically transferred into the uterus through the cervix. Transfers can be performed using cleavage or blastocyst stage embryos.

Additional Optional Procedures

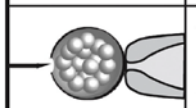
Gamete/Embryo freezing: Freezing occurs by slow-cooling or a rapid cooling method known as vitrification.



Surgical sperm retrieval: Sperm are aspirated from the epididymis or testis. In instances of low sperm count, larger portions of testicular tissue can be biopsied. ICSI is exclusively used for sperm obtained by sperm retrieval.

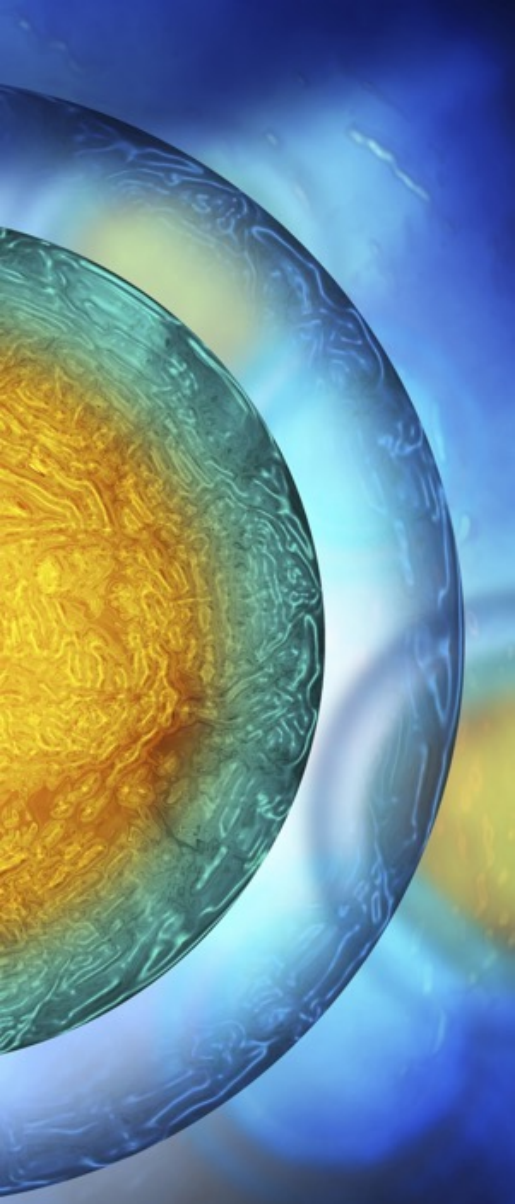


Preimplantation genetic diagnosis/ screening (PGD or PGS): Analyses for single genetic defects and aneuploidy are performed on a single blastomere (day 3 embryos) or trophectoderm cell (day 5 embryos). Trophectoderm biopsy is favored over blastomere biopsy, which has been shown to negatively affect embryo development. PGD was performed in 6% of ART cycles in the US.



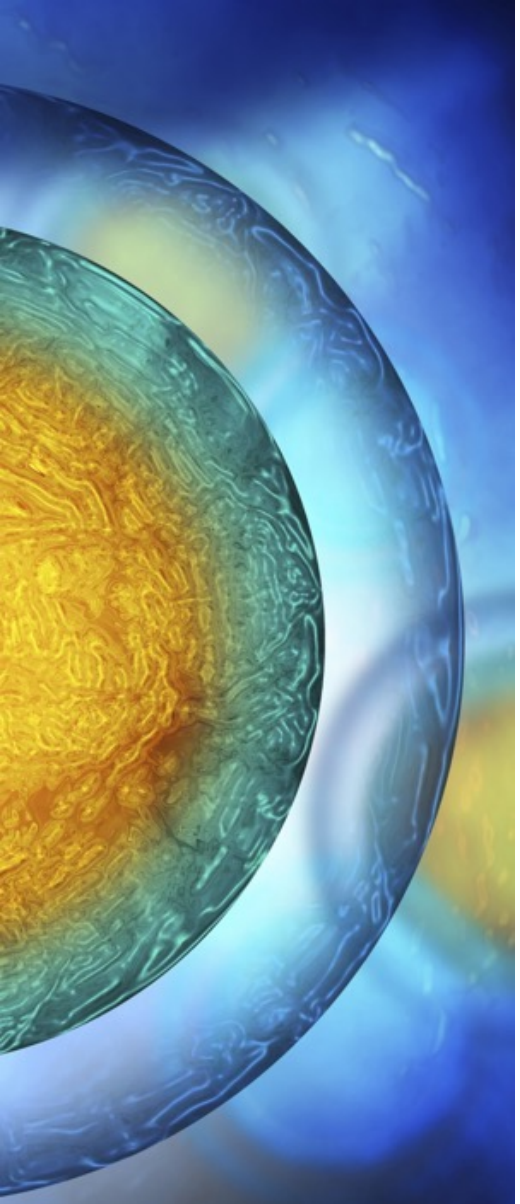
Assisted hatching: The outer barrier of the embryo, known as the zona pellucida, is manually or chemically penetrated, in hopes of improving implantation.

Vrooman & Bartolomei, Repro Toxicol, 2017



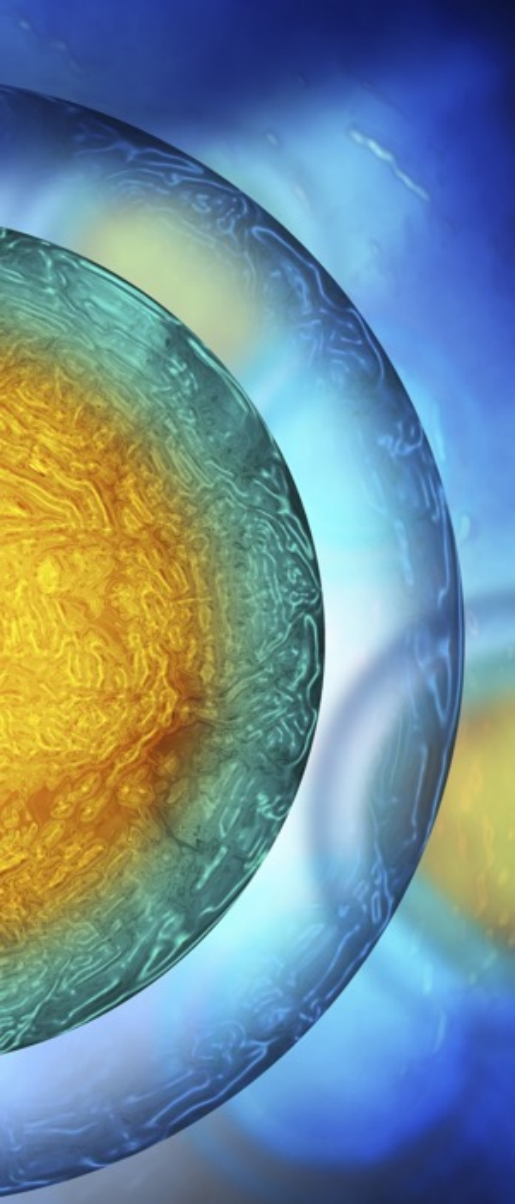
ART is associated with a higher risk of:

- Congenital anomalies
- Hypertensive disorders of pregnancy eg. pre-eclampsia
- Disorders of the placenta eg. placenta previa, placental abruption
- Preterm birth
- Low birth weight
- Perinatal mortality
- Small for gestational age
- Imprinting disorders



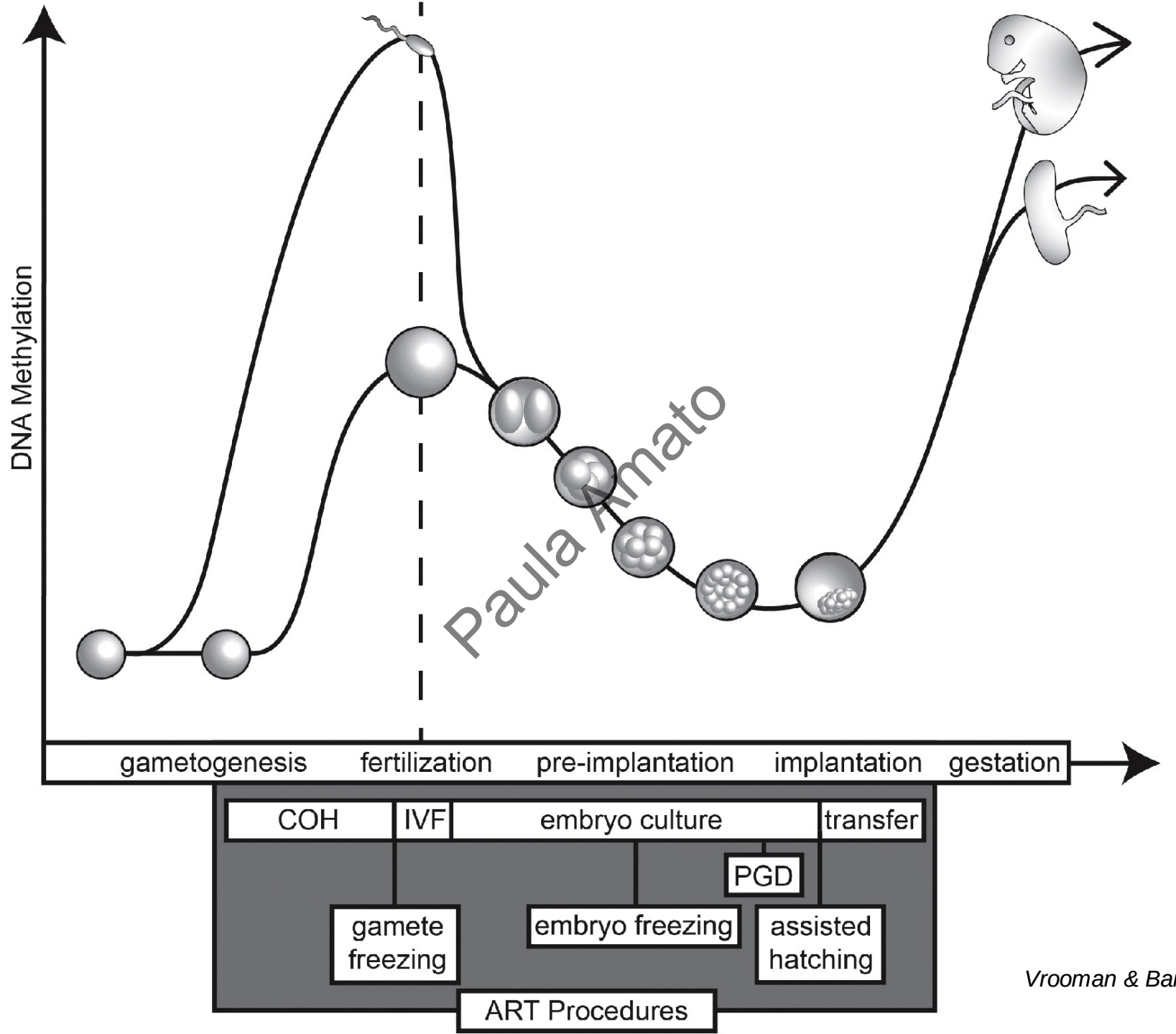
Potential Confounders

- Multiple gestation (statistical adjustment)
- Subfertility (fertile vs subfertile; ART vs non-ART vs spontaneous conception)

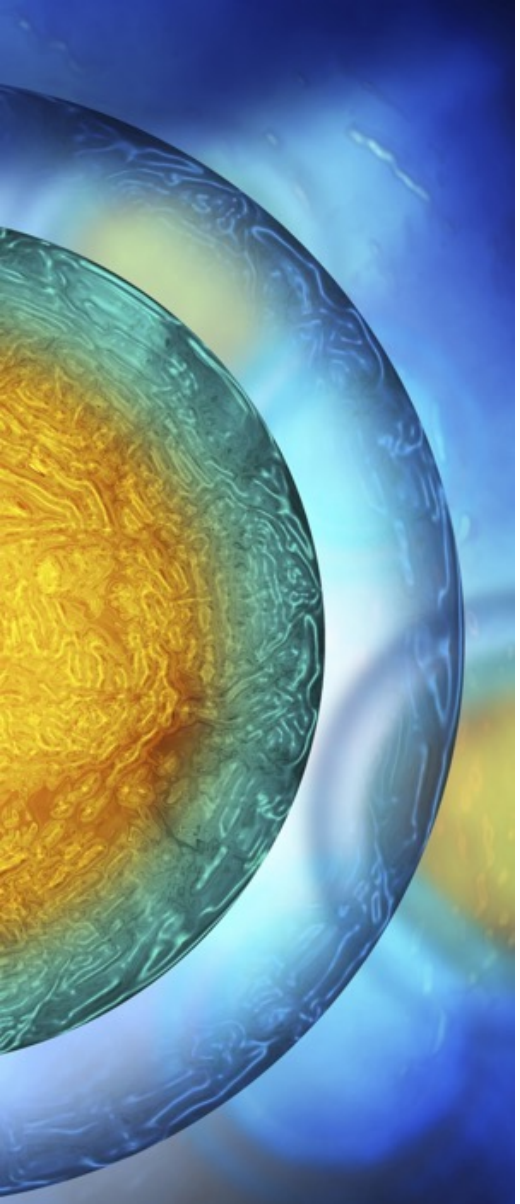


ART and the DOHaD Hypothesis

- ART is associated with increased risk of multiple gestation, preterm birth, and low birth weight
- LBW has been associated with CHD, HT, hyperlipidemia, DM
- Does “catch-up” growth can predispose to cardiometabolic complications in adulthood?

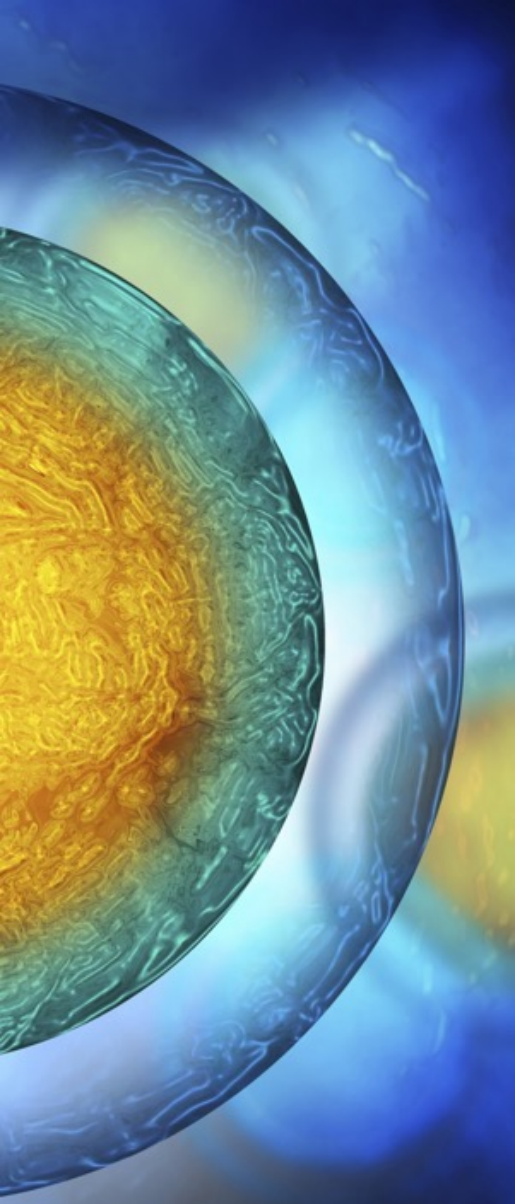


Vrooman & Bartolomei, Repro Toxicol, 2017



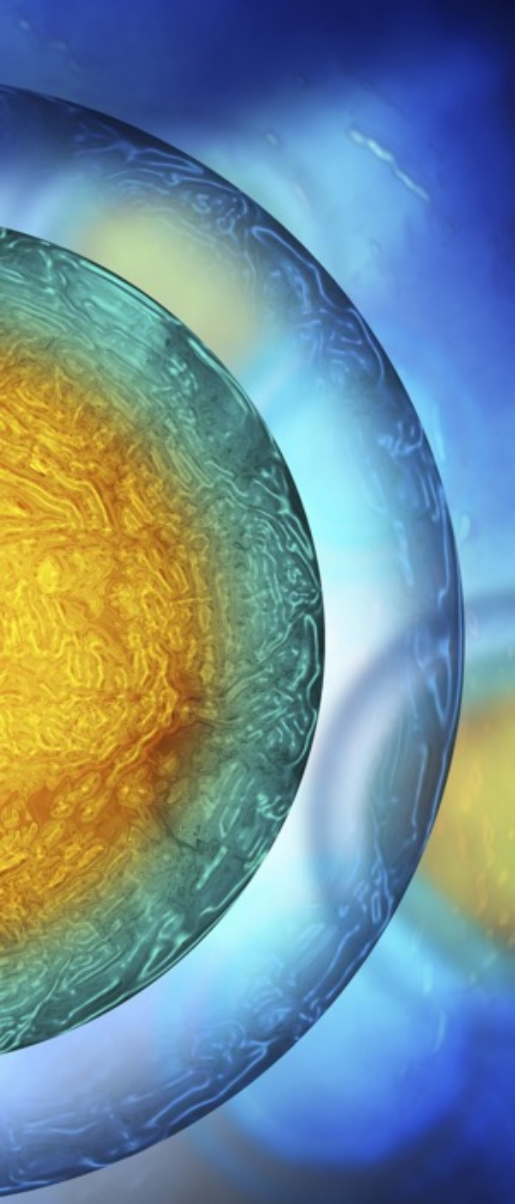
ART and the DOHaD Hypothesis

- *In-vivo* vs *in-vitro* exposures – mechanical stress, oxygen levels, temperature, pH, culture media and conditions
- Mechanism? – direct (embryo) vs indirect/adaptive (placenta) epigenetic changes
- Approaches - examination of epigenetic changes in candidate genes vs genome-wide changes in cord blood/placenta/early pregnancy tissue



ART and Congenital Anomalies

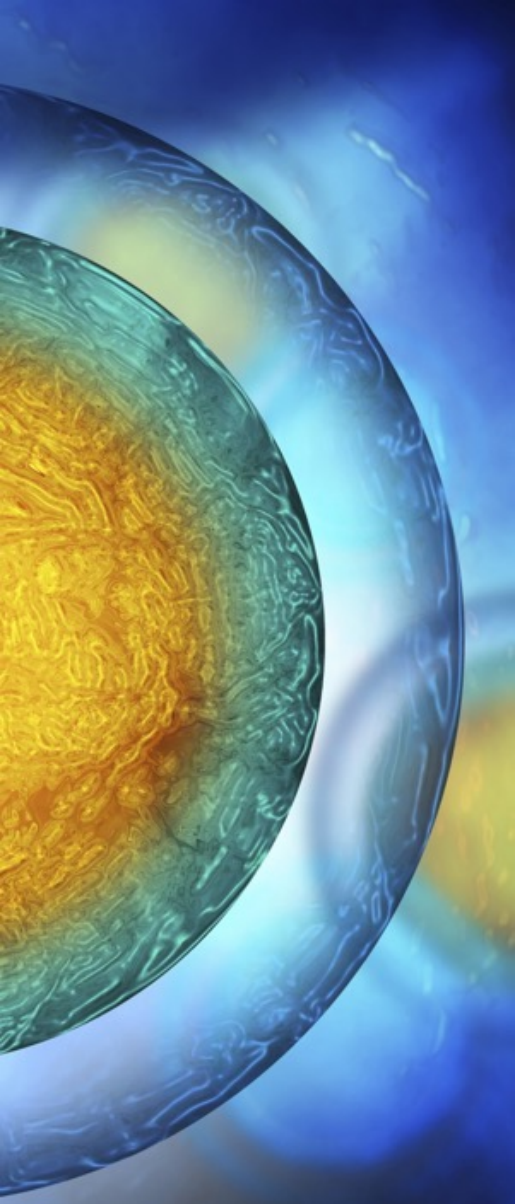
- ART is associated with a small increased risk of birth defects *(Davies et al, NEJM, 2012)*
- ICSI may be associated with a higher risk of birth defects than IVF
  - 70% of non-male factor cycles involve ICSI despite no improvement in LBR
- Higher risk of imprinting disorders eg. Beckwith-Wiedemann Syndrome, Angelman Syndrome (extended culture)
- Demethylation of ICRs (imprinting control regions)



Fresh vs Frozen Embryo Transfer

- Frozen ET had a lower risk of PTB, LBW, SGA, but a higher risk of macrosomia
- Frozen ET had higher rates of LBW, PTB, SGA, macrosomia, perinatal, neonatal, and infant mortality compared to spontaneous conception

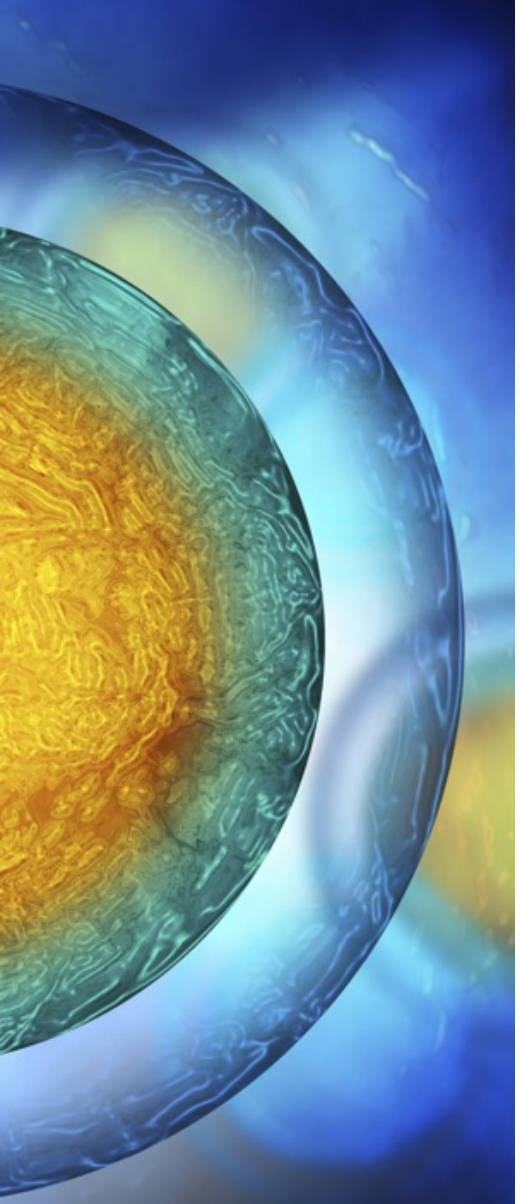
Wennerholm et al, Human Reprod, 2013



ART and Cardiometabolic Disorders

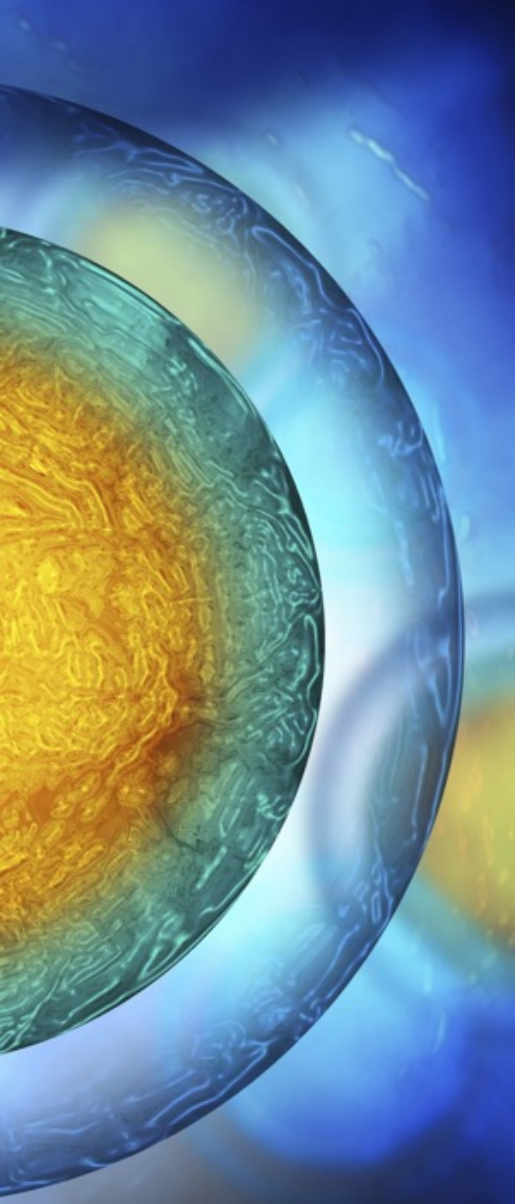
- Increased blood pressure in ART children
- Increased adiposity
- Impaired insulin sensitivity and glucose hemostasis
- Hyperlipidemia
- Adjusted for potential confounders; data is mixed; effect size is small; clinically significant?; no data in adults

Vrooman & Bartolomei, Repro Toxicol, 2017
Carpinello et al, Semin Rerpod Med, 2018
Feuer & Rinaudo, Healthcare, 2016



Summary

- Overall, ART appears safe; the majority of ART-conceived children are healthy
- There is a higher risk of adverse perinatal outcomes, but the absolute increase in risk is generally low
- The main adverse outcome of ART is multiple pregnancy; eSET is an effective risk reduction strategy
- Subfertility and ART likely both influence outcomes
- Implications for patient counseling



Future Research

- Longitudinal studies
- Mechanisms
- Interaction between genetics and ART
- Transgenerational effects

Thank You